I. REMARKS

Preliminary Remarks

This response is filed within the statutory deadline for response along with a petition for a three-month extension of time and the appropriate fee. The applicants respectfully request reconsideration and allowance of the present application.

Election

The applicants affirm the election of Group II, directed to claims 18 to 35, and the compound of claim 20.

Patentability Remarks

Rejections under 35 U.S.C. §102 –

Claims 18-35 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Hertel *et al.* (U.S. Pat. No. 6,103,910). The applicants respectfully traverse.

Hertel *et al.* describes the use of D-prolines in the treatment of disorders associated with amyloidosis, such as Alzheimer's disease and maturity onset diabetes mellitus (column 1, lines 19 to 26). In such diseases, a common pathological feature is the extracellular deposition of amyloid proteins, e.g., serum amyloid P protein (SAP). SAP is resistant to proteases and therefore plays a key role in the persistence of amyloid *in vivo*. For therapy, pharmaceutically active compounds have to be found that prevent the interaction of SAP with amyloid fibrils (column 4, lines 23 to 29). The D-prolines of Hertel *et al.* are such compounds. Inhibition of binding to amyloid fibrils is an attractive therapeutic target in a range of serious human diseases (column 4, lines 40 to 42).

It follows that Hertel *et al.* are concerned exclusively with the design of inhibitors which purportedly prevent the interaction of SAP with amyloid fibrils. In diseases such as Alzheimer's disease, unprotected amyloid fibrils present in brain tissue may then become the target of therapeutic intervention. Hertel *et al.* are therefore solely concerned with the localized inhibition of the SAP-amyloid fibril interaction using D-prolines according to formulae 1A or 1B.

In contrast, the present invention provides an agent for the depletion of an unwanted protein population from the plasma of a subject. This agent comprises a plurality of ligands that form complexes with a plurality of unwanted proteins (page 3, paragraph 3). These

complexes appear to be recognized by the body's own physiological mechanisms, which in turn clear and destroy these protein complexes. Thus the therapeutic activity of the present invention is different from that suggested by Hertel *et al.*

In addition, Hertel *et al.* merely provide a synthesis for D-prolines. There is no teaching or suggestion in Hertel *et al.* that these compounds can be used to complex unwanted proteins. Therefore, claims 18-35 are not anticipated by Hertel *et al.* and the applicants respectfully request removal of this rejection.

Hertel et al., U.S. Patent No. 6,103,910, is acknowledged in the present application as EP-A-0915088. Hertel is a disclosure confined to D-prolines and their use in treating disorders associated with amyloidosis, such as Alzheimer's disease and maturity onset diabetes mellitus (column 1, lines 19 to 26). D-prolines of two general formulae 1-A and 1-B are described in column 1, lines 31 to 49 as alternative generic structures which purport to form the basis of the Hertel invention. Hertel explains that in diseases such as Alzheimer's disease, a common pathological feature is extracellular deposition of so-called amyloid proteins in B-structured fibres (column 4, lines 20 to 21). Serum amyloid P component (SAP) is known to be a universal constituent of the abnormal tissue deposits in amyloidosis. SAP is resistant to proteases and therefore plays a key role in the persistance of amyloid *in vivo*. For therapy, pharmaceutically active compounds have to be found which would prevent the interaction of SAP with amyloid fibrils (column 4, lines 23 to 29). Hertel indicates in column 4, lines 40 to 42 that inhibition of binding to amyloid fibrils is an attractive therapeutic target in a range of serious human diseases.

It follows that Hertel is concerned exclusively with the design of inhibitors which purportedly prevent the interaction of SAP with amyloid fibrils. In a disease such as Alzheimer's disease, unprotected amyloid fibrils present in brain tissue may then become the target of therapeutic intervention. Hertel is therefore solely concerned with localized inhibition of the SAP-amyloid fibril interaction using D-prolines according to formula 1-A or formula 1-B.

In complete contrast, the present invention arises from the novel and surprising discovery that an unwanted protein population can be depleted from the plasma of a subject by the use of certain types of non-proteinaceous agent. Agents according to the invention comprise a plurality of ligands covalently co-linked so as to form a complex with a plurality of the proteins in the presence thereof. The ligands are capable of being bound by ligand binding sites present on the proteins.

Agents according to the invention do include a subset of the agents generically described in Hertel. However, the key to the present invention resides in the surprising discovery that where there are a plurality of ligands in the agent (*e.g.*, two in a "palindrome" compound), the protein target is actually cleared from the plasma of the subject. Accordingly, unwanted proteins such as those associated with a pathogenic effect and which are present in plasma may be effectively bound together by palindromic agents according to the invention so as to form a complex. Surprisingly, this complex appears to be recognized by the powerful mechanisms which exist in the body to detect and destroy proteins that are damaged, aggregated or misfolded. The purpose of the present invention is therefore to target specifically individual proteins and cause them to be identified by the body's own physiological mechanisms as requiring prompt clearance and destruction.

The present invention is therefore completely different from the treatment of amyloidosis described in Hertel. The therapeutic role that the disclosure of Hertel describes does not concern depletion of proteins from plasma. Instead, inhibitors are described, which have a localized inhibition action so as to prevent a protein from protecting its target. No inhibition is described or required according to the present invention. Furthermore, it is important to recognize that the disclosure of Hertel extends only to the synthesis of various compounds. While these compounds are suggested for use in the treatment of amyloidosis by inhibiting SAP binding, no actual therapeutic or experimental treatment of animals or humans is described in Hertel. There is therefore no disclosure or suggestion in Hertel that the use of any of the compounds described therein could possibly have resulted in complexation with a plurality of proteins, let alone form a complex which would be recognized by the body and promptly cleared. For at least these reasons, it is therefore respectfully submitted that the invention presently claimed is neither disclosed nor suggested by Hertel.

Claims 18-35 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Nitecki *et al.* (U.S. Pat. No. 4,895,872). The applicants respectfully traverse.

Nitecki *et al.* describe several immunosuppressive compounds that are analogues or derivatives of succinylacetone that are useful in treating patients suffering from diseases associated with hyperactive immune systems (column 2, lines 55 to 63). The only *in vivo* studies in Nitecki *et al.* involve an experimental model system in which adjuvant-induced arthritis in rats is used to test the immunosuppressive ability of succinylacetone and two succinylacetone derivatives (column 15). There is no teaching or suggestion in Nitecki *et al.* of using a plurality of ligands that form complexes with unwanted proteins nor of the

depletion of such proteins in plasma – as in the present invention. There is also no teaching that agents for the depletion of an unwanted protein population from the plasma of a subject may be provided, let alone any indication as to how such agents could be provided. Therefore, claims 18-35 are not anticipated by Nitecki *et al.* and the applicants respectfully request removal of this rejection.

Nitecki et al., U.S. Patent No. 4,895,972, is directed to the provision of immunosuppressive compounds that are useful in treating patients suffering from diseases associated with hyperactive immune systems, especially analogues or derivatives or succinylacetone (column 2, lines 55 to 63). Various derivatives of succinylacetone are described for this purpose. However, there appears to be no disclosure or suggestion of palindromic compounds according to the present invention, nor does there appear to be any disclosure or suggestion of the therapeutic treatment of the present invention. Indeed, the only *in vivo* work described in Nitecki relates to an experimental model system in which adjuvant induced arthritis in rates is used to test the effects of the succinylacetones described (column 15 – *in vivo* results). Nowhere in Nitecki is there any indication that agents for the depletion of an unwanted protein population from the plasma of a subject may be provided, let alone any indication as to how such agents could be provided. For at least these reasons, it is therefore respectfully submitted that the invention presently claimed is neither disclosed nor suggested by Nitecki.

Claims 18-35 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Watasuka *et al.* (U.S. Pat. No. 4,783,480). The applicants respectfully traverse.

Watasuka *et al.* describe 6-keto-prostaglandin derivatives that possess a useful level of cytoprotective activity associated with a low level of side effects (column 3, lines 18 to 20). There is, however, no teaching or suggestion in Watasuka *et al.* of using a plurality of ligands that form complexes with unwanted proteins nor of the depletion of such proteins in plasma. While Watasuka *et al.* suggest compounds for therapeutic use, there does not appear to be any teaching or suggestion of administration of the compounds to animal or human subjects. Therefore, claims 18-35 are not anticipated by Watasuka *et al.* and the applicants respectfully request removal of this rejection.

Wakatsuka et al., U.S. Patent No. 4,783,480, relates to novel 6-keto-prostaglandin E_1 derivatives which purportedly possess cytoprotective activity. It is acknowledged in column 1, lines 22 *et seq.* that prostaglandins are generally known to possess pharmacological properties including hypotensive activity, diuretic activity, bronchodilating

activity and antinidatory activity. Lines 29 *et seq.* indicate that if a prostaglandin is to be used in therapy, it is generally desirable to use only one pharmacological property. A need is therefore identified to provide prostaglandins which exert a selective action. Wakatsuka purportedly provides the identified novel prostaglandin derivatives which, according to column 3, lines 18 to 20, possess a useful level of cytoprotective activity associated with a lower level of side effects. As far as the applicant can determine, nowhere in this disclosure is there any indication or suggestion of palindromic compounds according to the present invention, let alone any disclosure or suggestion of the therapeutic effect to which the present invention relates. While Wakatsuka suggests compounds for therapeutic use, there again appears to be no disclosure of the administration of the compounds to animal or human subjects. For at least these reasons, it is therefore respectfully submitted that the invention presently claimed is neither disclosed nor suggested by Wakatsuka.

Finally, claims 18-35 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Adang (WO 98/50420). The applicants respectfully traverse.

Adang describes serine protease inhibitors that are useful in treating and preventing thrombin-mediated and thrombin-associated diseases (page 3, lines 19 to 20). Adang also describes the synthesis of some of these inhibitors and a few *in vitro* studies. Once again, there no teaching or suggestion in Adang of using a plurality of ligands that form complexes with unwanted proteins nor of the depletion of such proteins in plasma. In addition, Adang does not describe any *in vivo* experiments which describe the purported activity of the serine protease inhibitors.

Therefore, claims 18-35 are not anticipated by Adang and the applicants respectfully request removal of this rejection.

Adang, International Patent No. WO98/50420, relates to serine protease inhibitors useful for treating and preventing thrombin-mediated and thrombin-associated diseases including a number of thrombotic and prothrombotic states in which the coagulation cascade is activated (page 3, lines 19 to 21). Various examples describe the synthesis of the inhibitors and some *in vitro* assays of inhibitor activity are described. There appears to be no disclosure or suggestion of palindromic compounds according to the present invention, nor does there appear to be any disclosure or suggestion of the therapeutic treatment of the present invention. No *in vivo* work is described in which the purported activity of the serine protease inhibitors might have been tested. Accordingly, for at least these reasons, it is therefore

respectfully submitted that the invention presently claimed is neither disclosed nor suggested by Adang.

In conclusion, the applicants respectfully submit that none of the U.S. patents cited by the examiner, either individually or taken together, teach or suggest the present invention. In view of the foregoing, the claims are now believed to be in form for allowance, and such action is hereby solicited. If any point remains in issue that the examiner feels may be best resolved through a personal or telephone interview, the examiner is strongly urged to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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